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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,030	03/22/2006	David S. Garvey	0102258.00175US2	4436

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EXAMINER	
WARD, PAUL V	

ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
12/19/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/573,030	GARVEY ET AL.	
	Examiner	Art Unit	
	PAUL V. WARD	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 3/7/07 9/1/06.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I in the reply filed on September 18, 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Groups II-IV are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement, and reserved the right to file a divisional application to the non-elected subject matter.

Applicant is reminded to amend the claims to exclude the non-elected subject matter in accordance with the Restriction dated August 20, 2008.

An action on the merits on claims 1-27 is contained herein.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 7-13 and 19-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 7-13 and 19-23 are directed to a method of treating cardiovascular disease, restenosis, hypertension, cerebral infarction, atherosclerosis, myocardial infarction, platelet aggregation, congestive heart failure, renovascular disease, diabetes, disease resulting from oxidative stress, endothelial dysfunction, cirrhosis, osteoporosis, nephropathy, and a disease resulting from elevated levels of gamma-glutamyl transpeptidase. In light of this, it can be asserted that in spite of the vast expenditure of human and capital resources in recent years, no one drug has been found which is effective in treating all types of cardiovascular disease, restenosis, hypertension, cerebral infarction, atherosclerosis, myocardial infarction, platelet aggregation, congestive heart failure, renovascular disease, diabetes, disease resulting from oxidative stress, endothelial dysfunction, cirrhosis, osteoporosis, nephropathy, and a disease resulting from elevated levels of gamma-glutamyl transpeptidase. In re Hokum, 226 USPQ 353 (ComrPats 1985).

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include, but are not limited to:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

The breadth of the instant claims is seen to encompass methods for treating cardiovascular disease, restenosis, hypertension, cerebral infarction, atherosclerosis, myocardial infarction, platelet aggregation, congestive heart failure, renovascular disease, diabetes, disease resulting from oxidative stress, endothelial dysfunction, cirrhosis, osteoporosis, nephropathy, and a disease resulting from elevated levels of gamma-glutamyl transpeptidase with a therapeutically effective amount of the compound claimed by Applicant. Applicant has not defined the types of cardiovascular disease, restenosis, hypertension, cerebral infarction, atherosclerosis, myocardial infarction, platelet aggregation, congestive heart failure, renovascular disease, diabetes, disease resulting from oxidative stress, endothelial dysfunction, cirrhosis, osteoporosis, nephropathy, and a disease resulting from elevated levels of gamma-glutamyl transpeptidase. Thus, the claims appear very broad and the disclosure is not sufficient to provide enablement for the methods as claimed.

The nature of the invention

The nature of the invention is the treatment of cardiovascular disease, restenosis, hypertension, cerebral infarction, atherosclerosis, myocardial infarction, platelet aggregation, congestive heart failure, renovascular disease, diabetes, disease resulting from oxidative stress, endothelial dysfunction, cirrhosis, osteoporosis, nephropathy, and a disease resulting from elevated levels of gamma-glutamyl transpeptidase through the use of compounds and derivatives thereof. Currently, there are no known agents that treat these diseases inclusively or reduce the risk of cardiovascular disease, restenosis, hypertension, cerebral infarction, atherosclerosis, myocardial infarction, platelet aggregation, congestive heart failure, renovascular disease, diabetes, disease resulting from oxidative stress, endothelial dysfunction, cirrhosis, osteoporosis, nephropathy, and a disease resulting from elevated levels of gamma-glutamyl transpeptidase.

The level of predictability in the art

The treatment of cardiovascular disease, restenosis, hypertension, cerebral infarction, atherosclerosis, myocardial infarction, platelet aggregation, congestive heart failure, renovascular disease, diabetes, disease resulting from oxidative stress, endothelial dysfunction, cirrhosis, osteoporosis, nephropathy, and a disease resulting from elevated levels of gamma-glutamyl transpeptidase is highly unpredictable. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally

considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The amount of direction provided by the inventor.

The applicant has not demonstrated sufficient guidance provided in the form of administration profiles of the active agent or reference to the same in the prior art to provide a skilled artisan with sufficient guidance to practice the instant treatment of cardiovascular disease, restenosis, hypertension, cerebral infarction, atherosclerosis, myocardial infarction, platelet aggregation, congestive heart failure, renovascular disease, diabetes, disease resulting from oxidative stress, endothelial dysfunction, cirrhosis, osteoporosis, nephropathy, and a disease resulting from elevated levels of gamma-glutamyl transpeptidase claimed. Further, the applicant discloses that an effective amount of the compound will be administered without providing any direction other than that the compounds of the invention have a high therapeutic index and follows this with a definition readily found in a basic pharmacology textbook. It should be noted that the therapeutic index of a drug in humans is almost never known and is only determined through clinical experience previously recorded data or acceptable correlation to applicability in humans.

The existence of working examples.

There is not seen in the disclosure, sufficient evidence to support Applicant's claims of treating cardiovascular disease, restenosis, hypertension, cerebral infarction, atherosclerosis, myocardial infarction, platelet aggregation, congestive heart failure, renovascular disease, diabetes, disease resulting from oxidative stress, endothelial

dysfunction, cirrhosis, osteoporosis, nephropathy, and a disease resulting from elevated levels of gamma-glutamyl transpeptidase. A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 27 USPQ2d 1510 (CAFC). The disclosure does not demonstrate sufficient evidence to support the applicant's claim to the treatment and methods for reducing risk and inhibition. There are not sufficient working examples or data from references of the prior art to provide a nexus between those examples and a method of treating cardiovascular disease, restenosis, hypertension, cerebral infarction, atherosclerosis, myocardial infarction, platelet aggregation, congestive heart failure, renovascular disease, diabetes, disease resulting from oxidative stress, endothelial dysfunction, cirrhosis, osteoporosis, nephropathy, and a disease resulting from elevated levels of gamma-glutamyl transpeptidase with the claimed compound.

The level of one of ordinary skill.

The level of skill in this art is that of one with a doctoral understanding of treatment modalities and assessment of risk reduction in cardiovascular disease, restenosis, hypertension, cerebral infarction, atherosclerosis, myocardial infarction, platelet aggregation, congestive heart failure, renovascular disease, diabetes, disease resulting from oxidative stress, endothelial dysfunction, cirrhosis, osteoporosis, nephropathy, and a disease resulting from elevated levels of gamma-glutamyl transpeptidase therapeutics. Applicant's data is not convincing sufficiently

comprehensive or statistically to guide the skilled artisan in this field to practice the instantly claimed methods with compounds and pharmaceutical compositions comprising the claimed compounds feasible without undue experimentation.

The quantity of experimentation.

A great deal of experimentation is required in order for there to be a method of treating cardiovascular disease, restenosis, hypertension, cerebral infarction, atherosclerosis, myocardial infarction, platelet aggregation, congestive heart failure, renovascular disease, diabetes, disease resulting from oxidative stress, endothelial dysfunction, cirrhosis, osteoporosis, nephropathy, and a disease resulting from elevated levels of gamma-glutamyl transpeptidase. Furthermore, direction must be provided in the disclosure to enable the skilled artisan to determine which doses of the compounds claimed will be effect in treating conditions, diseases and reducing the risk of same. The references submitted do not demonstrate this. Therefore, one of ordinary skill in this art would require a significant amount of experimentation in order to determine the effective dosage to treat the multitudes of different types of cardiovascular disease, restenosis, hypertension, cerebral infarction, atherosclerosis, myocardial infarction, platelet aggregation, congestive heart failure, renovascular disease, diabetes, disease resulting from oxidative stress, endothelial dysfunction, cirrhosis, osteoporosis, nephropathy, and a disease resulting from elevated levels of gamma-glutamyl transpeptidase with the claim compounds.

Thus, it can be safely concluded that the instant case fails to provide an enabling disclosure for the treatment of cardiovascular disease, restenosis, hypertension,

cerebral infarction, atherosclerosis, myocardial infarction, platelet aggregation, congestive heart failure, renovascular disease, diabetes, disease resulting from oxidative stress, endothelial dysfunction, cirrhosis, osteoporosis, nephropathy, and a disease resulting from elevated levels of gamma-glutamyl transpeptidase.

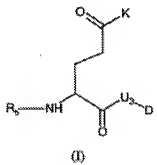
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1-6, 14-18 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Repolles Moliner et al. (U.S. Patent 6,800,612).

Applicant teaches nitrosated glutamic acid compounds with a general formula I:



(I)

wherein all the variables are as defined in the claim. Additionally, Applicant claims pharmaceutical compositions comprising the compound in formula I.

Repolles Moliner discloses nitrosated compounds and compositions, which share the same formulaic compounds. (See formula 1, col. 1). The compounds in the

said patent has the same structure, which includes D as H, U_3 as O, S(O) or N, R_b as a hydrogen or lower alkyl group, and W_3 is –C(O)-, -C(S)-, -T_3-, $(C(R_e)(R_f)_h$-, alkyl group, or $–(CH_2CH_2O)_{q1}$-, and falls within the range of Applicant's compounds. (See col. 2-26). Additionally, in column 22, lines 9-55, Repolles Moliner teaches pharmaceutical compositions comprising the compounds of formula I. Since Repolles Moliner teaches the exact compounds and compositions, Applicant's claims are anticipated, and thus, rejected under 35 U.S.C. 102(b).

2. Claims 1-6, 14-18 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Garvey et al. (WO 03/013432).

Garvey discloses nitrosated compounds and compositions, which share the same formulaic compounds. (See formula 1, Abstract). The compounds in the said patent has the same structure, which includes D as H, U_3 as O, S(O) or N, R_b as a hydrogen or lower alkyl group, and W_3 is –C(O)-, -C(S)-, -T_3-, $(C(R_e)(R_f)_h$-, alkyl group, or $–(CH_2CH_2O)_{q1}$-, and falls within the range of Applicant's compounds. (See pp. 16-22). Additionally, on pages 30-33, Garvey teaches pharmaceutical compositions comprising the compounds of formula I. Since Garvey teaches the exact compounds and compositions, Applicant's claims are anticipated, and thus, rejected under 35 U.S.C. 102(b).

3. Claims 1-6, 14-18 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Scaramuzzino, Giovanni. (EP 1336602).

Scaramuzzino discloses nitrosated compounds and compositions, which share the same formulaic compounds. (See formula 1, Abstract). The compounds in the said

patent has the same structure, which includes D as H, U_3 as O, S(O) or N, R_b as a hydrogen or lower alkyl group, and W_3 is –C(O)-, -C(S)-, -T_3-, $(C(R_e)(R_f)_h$-, alkyl group, or $-(CH_2CH_2O)_{q1}$-, and falls within the range of Applicant's compounds. (See pp. 4-18). Additionally, on pages 28-31, Scaramuzzino teaches pharmaceutical compositions comprising the compounds of formula I. Since Scaramuzzino teaches the exact compounds and compositions, Applicant's claims are anticipated, and thus, rejected under 35 U.S.C. 102(b).

4. Claims 24-26 are rejected because they are dependent upon a rejected base claim.

Conclusion

Claims 1-27 are pending. Claims 1-27 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to PAUL V WARD whose telephone number is 571-272-2909. The examiner can normally be reached on M-F 8 am to 4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/PAUL V WARD/
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624